REMARKS

Upon entry of the foregoing amendment, claims 11-25 are pending. Claims 1-10 have been cancelled.

The foregoing amendment to the specification inserts AMENDED SHEETS 3 and 3bis which were submitted during prosecution of the international application with the IPEA.

Claims 1-10 have been canceled without prejudice and replaced with new claims 11-25 to more particularly point out and distinctly claim the invention under U.S. patent practice.

Support for the preferred range of 9.0% to 14.30% of the alkalizing agent in new claim 11 can be found in the examples in the present specification. For example, the amount of alkalizing agent used in Example 1 was 14.3%, whereas in Example 12X, 9.0% of alkalizing agent was used (60/670 mg). All of the examples in the present specification are clustered within the 9.0% to 14.3% range for the alkalizing agent (with the sole exception of Example 3), thus defining the preferred range and the minimum/maximum values of the disclosed examples.

Support for cetirizine in claims 12 and 25 can be found on page 5, lines 20-24 of the present specification.

No new matter has been added to the specification or to the claims. Please find attached a marked-up version of the specification entitled "Version with Markings to Show Changes Made".

The Present Invention in View of the Prior Art Cited in the Parent Application

The Claimed Invention

The claimed invention relates to a pharmaceutical composition, having at least one excipient comprising a matrix and an alkalizing agent, which can be administered orally and allows for the controlled release of at least one active substance. This pharmaceutical composition comprises said at least one active substance, between 5 and 60% by weight of an excipient selected from hydrophilic, lipophilic and/or inert matrices, and between 9 and 14.3% of an alkalizing agent selected from alkali or alkaline-earth metal hydroxides, carbonates, bicarbonates, phosphates, sodium borate and basic salts of organic acids.

This novel oral pharmaceutical composition allows for the regular and continuous release of pharmaceutically active substances such that effective therapeutic treatments are observed over long periods of time in, for example, only one or two doses, without requiring excessive quantities of matrix excipients.

The Present Invention as Compared to Norling

The most relevant reference cited in the parent application is Norling (WO 95/34291 A1).

Norling relates to a drug delivery system in the form of pellets and discloses multiple unit formulations of hard solid spherical cores of an inert carrier. Norling does not disclose any Example which reads on the present invention. Although Norling discloses a list of twelve inorganic substances to be used as inert carriers (Norling, page 3, lines 7-15), the inert carrier in Norling could be any one of the twelve specified inorganic substances, two of which are sodium bicarbonate and magnesium carbonate.

However, Applicants would like to draw the Examiner's attention to Norling, page 3, lines 7-15; page 21, lines 8-21; page 79, lines 5-10; and page 84, lines 9-15, wherein Norling requires the disclosed composition to contain the inert carrier (e.g., sodium bicarbonate/magnesium carbonate) in at least 20% or more by total weight of the composition. In contrast, new claim 11 expressly recites the alkalizing agent in the claimed invention to be limited to between 9 and 14.3%. Thus, in its broadest disclosure, the inert carrier in Norling would have a concentration from 20% and upwards which exceed the amount of alkalizing agent recited in the present invention's claim 11. Moreover, Norling's Examples use even much higher amounts of 75% or more. (See Examples in Norling)

Since claim 11 limits the amount of alkalizing agent present to be between 9 and 14.3%, which is much less than the minimum amounts of 20% required for the inert carriers in Norling, Norling does not disclose or teach the present invention at all.

Nor does Norling suggest the present invention or render the instant claims obvious.

The concentration of inert carrier disclosed even generically in Norling (>= 20%) is now explicitly outside the range in claim 11. But in any event such broad ranges in Norling cannot be

considered fully enabling or properly disclosed. The only teaching for low concentrations (20%, 30% 50% etc) is two lines (page 4, line 10-11) in Norling out of a specification which is 87 pages long! All the examples and subsequent teachings on page 4 suggest that in fact much higher concentrations of inert carrier are required (over 75%). Certainly, in practice, one skilled in the art upon reading Norling is taught away from using low concentrations of the inert carrier (e.g. 14.3%) notwithstanding a nominal and purely theoretical disclosure of amounts of 20% or 30%. There is very ample teaching in Norling to persuade a skilled reader to avoid formulations lower than the minimum specified value of 20% for inert carrier.

Also, both magnesium carbonate and sodium bicarbonate are disclosed in Norling as **inert carriers** selected from said list of twelve inorganic substances, are not exemplified and would be used in different amounts as **alkalizing agents**, as claimed herein. Therefore, these two carriers cannot be considered fully enabled since Norling teaches that the carriers therein are inert (see, e.g., page 4, line 10 of Norling) and thereby cannot render the present invention obvious.

On the other hand, Applicants have demonstrated that, very surprisingly, soluble alkalizing agents can be used as active agents in order to obtain prolonged release pharmaceutical forms. Although soluble inert carriers are permitted (but not preferred) in Norling (see page 9, lines 4-8), they are disclosed to permit their use in non-preferred preparation processes where non-aqueous media are used to form Norling-type formulations. Accordingly, solubility in inert carriers is taught as a disadvantage in Norling and consequently, inert carriers are not present in any of the final formulations or examples. Of course, this is quite different from the present invention wherein the alkalizing agent must have sufficient solubility in an aqueous phase at physiological pH, i.e. during use of the formulation. Thus, the amount of soluble ingredients and permitted solubility would be completely different in the present invention as compared to Norling.

Also, cellulose-type excipients in Norling are stated to have various functions such as, for example, as fillers, disintegrants and/or binders. These specific cellulosic materials are usually very different from the matrix materials used in the present invention. HPMC, which may be used as a matrix excipient in the present invention is disclosed generically only as a binder in Norling. However, there is a difference between a matrix excipient and a binder, which is foreshadowed in

the present invention in which binders are listed as separate optional ingredients i.e. which perform another function from the matrix (See e.g., claim 15 of the present invention). Matrices form an extended network within which the active ingredient is slowly released in th present invention. In contrast, a binder is present in much smaller amounts and acts simply to hold the ingredients together.

Accordingly, use of HPMC as a binder does not suggest at all its use as a matrix since one in the art would formulate the HPMC in different amounts to be suitable for each of these entirely different uses.

In summary, Norling does not suggest the present invention because, *inter alia*, Norling does not provide any enablement for magnesium carbonate and sodium bicarbonate (inert carriers in Norling) as alkalizing agents; the inert carriers themselves are not even preferred and none of them are present in any of Norling's examples; excipients in matrix form are not suggested by Norling; and Norling actually teaches away from the claimed limitation regarding the concentration of the alkalizing agent being less than or equal to14.3% (usually it greater than 75% in Norling).

The Present Invention in View of Kwan and Norling

Kwan (WO 94/09761A1) is less relevant than Norling. In addition, there is no motivation to combine Kwan with Norling.

Kwan may teach coating a matrix core with a drug in order to achieve both, an immediate release of the drug in the coating, and a sustained release of the drug in the matrix core. However, there is no motivation from the prior art of record to combine Kwan with Norling to attain the present inventive pharmaceutical composition.

Moreover, even if motivation did exist to combine Norling and Kwan, the references in combination do not provide the present inventive pharmaceutical composition as recited in the instant claims. Norling does not comply with the limitation regarding the composition comprising a water-*soluble* alkalinizing agent. Norling instead discloses compositions comprising water-

insoluble carriers. Moreover, Norling does not disclose the alkalizing agent to be between 9 and 14.3% by weight as recited in the present claims.

Norling teaches generically that many different coatings could be used with their multiple dose forms, but there is no motivation for a reader to select the Kwan reference rather than any other one of the many (hundreds) of others references to optional coatings in this field. As Norling already relates to a formulation with a multiple dose form, it would be superfluous for a skilled reader of Norling to refer to Kwan which solves this problem in a different way and are inferior formulations.

Norling also teaches that it is an object of the invention that the formulations therein are independent of administration route, whereas Kwan is concerned with oral compositions only. This provides a further disincentive of a reader of Norling to refer to the inferior formulations of Kwan. Hindsight is being used to arrive at claims 17 -20 of the present invention by an arbitrary combination of features from two arbitrarily selected references.

Therefore, to arrive at the present invention, one of ordinary skill in the art upon reading Norling would have to perform the following steps, each contrary to the teaching therein, making arbitrary selections of often solely generic, non-enabled disclosures:

a) select at least one or the 2 of the least preferred of the 12 inert carriers recited in Norling ($MgCO_3$, $NaHCO_3$) rather than any of the others, said inert carriers not even preferred in Norling;

b) formulate these in amounts much less (between 9 and 14.3% by wt.) than the extreme minimum amount (20%) specified in Norling;

c) combine these with a matrix ingredient (not taught in Norling at all);

d) formulate the matrix in a manner different from that for binder ingredients taught in Norling;

e) ensure the final formulation was water-soluble at physiological pH (not suggested in Norling) notwithstanding that all the examples in Norling are insoluble and that Norling teaches that carriers to be inert;

f) apply the formulation specifically for oral use rather than any other of the many delivery methods suggested in Norling.

g) cross refer an arbitrary reference (Kwan) to arrive at the double layered tablets of the present invention (claims 17 to 20) despite a disincentive to do so.

Thus, Norling and Kwan do not teach or suggest, either separately or in combination, a pharmaceutical composition administered orally which allows for the controlled release of an active substance comprising at least one active substance, between 5 and 60% by weight of an excipient, and between 9 and 14.3% by weight of at least one alkalinizing agent which is water-soluble under physiological pH conditions, and the process for making thereof.

Favorable action on the merits is solicited.

Respectfully submitted,

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